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08/215,030

| SERIAL NUMBER | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/215,030 | 03/18/94 | TAMARKIN | L 019940021 |

EXAMINER

18N1/0714

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1813 | 7 |

DATE MAILED: 07/14/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on Election 4-24-95 ☐ This action is made fina

A shortened statutory period for response to this action is set to expire three month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____

**Part II SUMMARY OF ACTION**

1. ☑ Claims 8-22 are pending in the application
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims 1-7 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 8-22 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Applicants' election of Species I (IL-2) in paper No. 6 is acknowledged. However, upon reconsideration the species election has been withdrawn.

The disclosure is objected to because of the following informalities:

It appears that vascular epithelial growth factor (VEGF) on page 5 of the specification should be endothelial growth factor according to the abbreviation commonly used in the art and the fact that it is endothelial cells rather epithelial cells which line blood vessels. Appropriate correction is required.

Claims 8-22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "toxic biologically-active factor" in claims 8, 15, and 19 is confusing because most of the claimed factors are normally present in the body and therefore are not toxic. While the specification defines toxicity to include various responses such as fever, edema, shock, etc. (p 5), it appears that these reactions to the biologically active factors would be a dose-dependent response rather than an inherent property of the normally present factors.

In claims 9, 16, and 20 it appears that vascular epithelial growth factor (VEGF) should be vascular endothelial growth factor for the reasons discussed above.

Claim 15 is vague because it is drawn to a method of reducing the toxicity of a normally toxic biologically active factor in a vaccine comprising administering a colloidal metal with a

toxic biologically active factor. However, the claim does not actually recite the administration of the vaccine. It is not clear whether the toxic biologically active factor is the vaccine or whether the toxic biologically active factor is administered with a vaccine. If the toxic biologically active factor is administered with the vaccine then the role of this factor in the composition is not clear.

In claim 19, it is not clear whether "immune disease" is meant to identify autoimmune diseases or other diseases associated with the immune system such as allergy, graft rejection, dermatologic delayed type hypersensitivity, immunodeficiency diseases, etc.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The invention is directed toward methods of reducing the toxicity of a biologically active factor by administering the factor with colloidal gold. The specification discloses that interleukin-2 (IL-2) displays significant therapeutic results in the treatment of renal cancer but that the toxic side effects result in the death of a significant number of the patients. The specification describes that if IL-2 is mixed with colloidal gold, little or no toxicity is observed and a strong immune response occurs (p. 9, lines 21-30). The specification teaches that colloidal

gold also reduces the toxicity of lipopolysaccharide in mice (p 13). The specification teaches that anti-IL-2 antibodies are generated when an IL-2-colloidal gold mixture is administered to rabbits and anti-IL-6 antibodies are generated when an IL-6-colloidal gold mixture is administered to mice (p 10-11 and p 13-14). The specification teaches that colloidal gold may be used as a putative adjuvant for generating antibodies against endogenous toxins as well as cytokines thought by be involved in sepsis cancer, cachexia and metastasis (p 14).

Because the administration of two biologically active factors, IL-2 and interleukin-6 (IL-6), with colloidal gold results in the formation of antibodies against these cytokines, it is unclear whether the biological activity of these cytokines and other biologically active factors would be maintained when administered *in vivo* due to the formation of antibodies which would be expected to bind and neutralize the biologically active factors. Kirchner et al teach that while the emergence of neutralizing antibodies to recombinant interleukin-2 (rIL-2) and natural interleukin-2 (nIL-2) is not very common, the incidence of antibody formation can be effected by various factors including the dose regimen, duration of therapy, cumulative dose, and route of administration (p 1863, column 2). Kirchner et al teach that the possible clinical impact of antibody development is unclear, but a particular concern is that the antibody formation may coincide with an abrogation of biologic and clinical response (paragraph bridging pages 1863-1864). Kirchner et al describe that a significant decrease in biologic activation was noted during the emergence of neutralizing antibodies to rIL-2 in one patient (p 1864). As taught by Kirchner et al above, various factors can effect antibody formation to IL-2. While the administration of IL-2 alone only occasionally results in the formation of neutralizing antibodies, it is unclear

whether the administration of colloidal gold as an adjuvant would increase the formation of these antibodies thereby decreasing the biological and therapeutic activity of the factors. In addition, Balkwill teach that cytokines interact in a network and that they induce each other, modulate other cytokine cell surface receptors, and have synergistic, additive or antagonistic interactions on cell function (p 299). Roitt et al teach that cytokines are communication links within the immune system and between the immune system and other organs (Fig 8.26 on page 8.15). Because the activities of cytokines are interconnected and affect various organ systems, the overall result of the formation of antibodies against one particular cytokine or biologically active factor on the immune system and other organ systems is unpredictable. The specification does not provide guidance on how to use the compositions such that the biologically active factors would maintain therapeutic effects when administered with colloidal gold. Because the effects of the formation of antibodies to the biologically active factors on their therapeutic activity is unpredictable, it would require undue experimentation to determine conditions under which the biologically active factors could be used with colloidal metals such that they would retain their therapeutic activity.

The specification discloses that IL-2 administered to nude mice reduced implant tumor size, but killed the animals (p 12). The specification teaches that in the mice receiving colloidal gold with IL-2 there was an increase in B and T cell function and an increase in NK activity (p 12). However, the specification does not teach that the IL-2-colloidal gold mixture maintains the ability to reduce implant tumor size. Due to the formation of antibodies to IL-2 as a result of its administration with colloidal gold, it is not predictable whether the IL-2 would maintain the

ability to reduce the implant tumor size. The specification teaches that when IL-1 is mixed with colloidal gold, it retains its ability to inhibit the growth of human breast cancer cells (MCF-7) *in vitro*. However, the results of this particular *in vitro* assay are not relevant in addressing the issue of whether the colloidal gold mixture with biologically active factors results in a loss of activity of the factors due to the formation of antibodies because antibodies against the factors would not be formed in the *in vitro* MCF-7 assay and therefore the effects of the antibodies cannot be measured in this system.

The invention is drawn to reducing the toxicity of biologically active factors in a vaccine. However, with the exception of endotoxin and lipid A, the claimed cytokines and growth factors are not recognized as components of pathogens and therefore an antibody response generated against these factors would not be expected to provide protection against disease associated with a particular pathogen. The invention is also drawn to administering a therapeutically effective amount of a composition of colloidal gold and a biologically active factor to a human or animal with cancer or an immune disease. The role of many of the claimed biologically-active factors in treating cancer and immune diseases is unpredictable because of the multiple and varied biological functions of these factors. In addition, the role of the wide variety of claimed biological substances, including cytokines, growth factors, lipid A, endotoxin, phospholipase, heat shock proteins, and Rh factors in immune diseases such as autoimmune diseases, allergy, delayed type hypersensitivity, immunodeficiency disease and other diseases related to immune function is not known. The specification does not provide guidance on determining which of the biologically active factors to use for various cancers or immune diseases and it would require

undue experimentation to identify the factors which would be effective for treating cancer or immune diseases and for use in vaccines and to determine conditions under which they could be used in the presence of antibodies formed *in vivo* such that they would maintain their therapeutic activity.

Claims 8-22 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 12, 14, 15 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Shiosaka et al.

Shiosaka et al teach administering a composition containing an admixture of a colloidal metal and biologically active factors (which may be toxic) such as histamine, peptide hormones, steroids, amino acids, proteins and glucoproteins. Shiosaka et al teach that administration of the composition elicits an immunological response to the biologically active factor (column 1 lines 64 to column 2 line 4 and column 2 lines 54-68 and column 3 lines 33-35 and lines 50-54).

Shiosaka et al specifically teach subcutaneous administration of the composition in multiple doses (column 3, lines 50-55).

While Shiosaka et al do not teach that the toxicity of the biologically active factor is reduced by the administration of the composition, the method steps taught by Shiosaka et al are identical to the claimed method steps and therefore the method would inherently perform the same function (i.e. reducing toxicity of the biologically active factors). Claims 15 and 18 are included in the above rejection because the method steps of claims 8 and 15 are identical.

Claims 8, 12, 14, 15 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Tomii et al.

Tomii et al teach the multiple subcutaneous administrations of an admixture of colloidal gold and platelet-activating factor (PAF) such that the composition elicits the production of antibodies (p 75-79).

While Tomii et al do not teach that the toxicity of PAF is reduced by the administration of the composition, the method steps taught by Tomii et al are identical to the claimed method steps and therefore the method would inherently perform the same function (i.e. reducing toxicity of PAF). Claims 15 and 18 are included in the above rejection because the method steps of claims 8 and 15 are identical.

Claims 19 and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Scheinberg.

Scheinberg teach the administration of an admixture of colloidal gold and a sulfhydryl compound to patients with rheumatoid arthritis in multiple doses in order to decrease the toxicity of the treatment (column 3, lines 31-40, column 8, lines 25-44 and column 9, lines 45-50).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 8-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Shiosaka et al.

Shiosaka et al teach administering a composition containing an admixture of a colloidal metal and biologically active factors (which may be toxic) such as histamine, peptide hormones,

steroids, amino acids, proteins and glucoproteins. Shiosaka et al teach that administration of the composition elicits an immunological response to the biologically active factor (column 1 lines 64 to column 2 line 4 and column 2 lines 54-68 and column 3 lines 33-35 and lines 50-54). Shiosaka et al teach that the binding of proteins and glucoproteins to colloidal medal particles make the production of antibody against that substance easy (column 2, lines 54-60). Shiosaka et al teach subcutaneous administration of the composition in multiple doses (column 3, lines 50-55).

While Shiosaka et al do not teach that the toxicity of the biologically active factor is reduced by the administration of the composition, the method steps taught by Shiosaka et al are identical to the claimed method steps and therefore the method would inherently perform the same function (i.e. reducing toxicity of the biologically active factors). Shiosaka et al do not specifically teach the administration of the claimed biologically active factors. Shiosaka et al do not teach the administration in a single dose or by an intravenous or intramuscular route.

It would have been obvious to one of ordinary skill in the art to administer the claimed biologically active factors in an admixture of colloidal metals because admixtures of proteins or glucoproteins and colloidal metal particles have enhanced capability of antibody production as taught by Shiosaka. It would have been obvious to administer biologically active factors that are associated with pathogens such as endotoxin and lipid A with colloidal metal particles because these particles enhance antibody production as taught by Shiosaka and the administration of the composition would be expected to have an adjuvant effect when administered as a vaccine. It would also have been obvious to administer the composition with intravenously or intramuscularly

because both are common routes of administration for the administration of antigens and vaccines. Optimization of the number of doses for maximum antibody response would constitute routine experimentation and be within the skill of the ordinary artisan.

Claims 8-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Tomii et al.

Tomii et al teach the multiple subcutaneous administrations of an admixture of colloidal gold and platelet-activating factor (PAF) such that the composition elicits the production of antibodies (p 75-79). Tomii et al teach that colloidal gold acts as a hapten-carrier to obtain anti-hapten antibodies with no reactivity to the carrier (p 79).

While Tomii et al do not teach that the toxicity of PAF is reduced by the administration of the composition, the method steps taught by Tomii et al are identical to the claimed method steps and therefore the method would inherently perform the same function (i.e. reducing toxicity of PAF). Tomii et al do not specifically teach the administration of the claimed biologically active factors. Tomii et al do not teach the administration in a single dose or by an intravenous or intramuscular route.

It would have been obvious to one of ordinary skill in the art to substitute claimed biologically active factors in the method of administering a admixture of colloidal metal and platelet-activating factor in order to generate antibodies to the biologically active factors because the colloidal metal acts as a carrier for the production of antibodies as taught by Tomii et al. It would have been obvious to administer biologically active factors that are associated with pathogens such as endotoxin and lipid A with colloidal metal particles because these particles

enhance antibody production as taught by Tomii et al and the administration of the composition would be expected to have an adjuvant effect when administered as a vaccine. It would also have been obvious to administer the composition with intravenously or intramuscularly because both are common routes of administration for the administration of antigens and vaccines. Optimization of the number of doses for maximum antibody response would constitute routine experimentation and be within the skill of the ordinary artisan.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Goldstein et al, Lipids 26(12):1250-1256, 1991 and Hisamatsu et al, Lipids 26 (12):1287-1291, 1991. Both Goldstein et al and Hisamatsu et al teach that platelet activating factor is toxic.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie K. Staples whose telephone number is (703) 305-7556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission via the PTO Fax Center, located in Crystal Mall 1. The Fax Center number is (703) 305-7939. The faxing of such papers must conform to the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989).

JKS
Julie K. Staples, Ph.D.
July 11, 1995

MICHAEL P. WOODWARD
PRIMARY EXAMINER
GROUP 1800